DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 12/29/2009 is acknowledged. With respect to the first election requirement, Applicant elects with traverse (A) a lipid with a positive net charge from claim 50 and further elects the quarternary ammonium group of claim 53. With respect to the second election requirement, Applicant elects a therapeutic agent and further elects the therapeutic agent camptothecin.

The restriction requirement mailed 3/4/2009 stated that Group I, directed to a non-vesicular preparation, encompassed claims 47-74. However, claims 70-71 and 73-74 properly belong in Group III, directed to a method of producing a non-vesicular preparation. Therefore Group I should not properly encompass claims 70-71 and 73-74. In a telephone interview on 4/20/2010, Applicant agreed to proceed with examination with the understanding that claims 70-71 and 73-74, which are the subject matter of non-elected Group III, will be currently withdrawn.

Applicant traverses the rejection. The traversal is on the ground(s) that there is no undue burden to search the inventions together. This is not found persuasive because search burden is not a criterion used to establish the propriety of restriction in applications filed under 35 U.S.C. 371. The standard is unity of invention. The instant application lacks unity of invention for the reasons set forth in the restriction requirement.

Regarding the election of species, Applicant traverses on the ground that the camptothecin, taxane, and epothilone, at minimum, should be examined as the species of therapeutic agent as they are all related as lipophilic cytostatic anti-tumor agents. This is not persuasive because these species, although they are related as lipophilic cytostatic anti-tumor agents, have different molecular structures, different pharmacological behavior, and are not obvious variants over each other.

The requirement is still deemed proper and is therefore made FINAL.

The Examiner reminds Applicant that restriction has been made between product and process claims. Where Applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder.

The Examiner further reminds Applicant that when the elected species, camptothecin, is held to be allowable, the search will be expanded to non-elected embodiments.

In the search for the elected species, prior art directed to non-elected embodiments was discovered. This discovery is not an indication that the full scope of the claims have been examined.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 47-51, 53-67, and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what components/requirements are optional following the second "optionally" in claim 47. It is unclear what is optional following "optionally at least one stabilizing agent…". Is everything that follows "optionally" optional: "at least one stabilizing agent in a concentration of about 10 mM to about 600 mM in an aqueous phase, wherein said preparation is transparent, isotropic and substantially homogenous"? Is it only the at least one stabilizing agent in a concentration of about 10 mM to about 600 mM that is optional? Is it only the at least one stabilizing agent in a concentration of about 10 mM to about 600 mM in an aqueous phase that is optional? The claim language leaves multiple interpretations for what is and is not optional following the second "optionally".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 47-51, 53-60, and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Felgner et al (Lipofection: A highly efficient, lipid-mediated DNA-transfection procedure, Proc. Natl. Acad. Sci, 1987, 84, 7415; document already in record). Felgner et al discloses a 15 mM acetonitrile solution of N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) (15 mM calculated from (10/670)/.001 where 670 is the molecular weight of DOTMA) (see page 7413, col 2, DOTMA Synthesis and Liposome Preparation). DOTMA is a cationic amphiphile and contains N-[1-(2,3-diacyloxy)propyl]-N,N,N-trimethyl ammonium (see Figure 1), the compound disclosed in instant claim 53. The lipid is in solution (as oppose to a suspension, emulsion, etc), and would reasonably be transparent, isotropic, and substantially homogeneous, as these properties are inherent in liquid solutions. As water is absent from the solution, the DOTMA/acetonitrile solution would be a non-vesicular preparation. Claim 47 recites “in an aqueous phase”. It is unclear if this is a required claim limitation (see ***Claim Rejections - 35 USC § 112, Second Paragraph*** above). For the purposes of comparing the claims to the prior art, the Examiner interprets “in an aqueous phase” in instant claim 47 to be optional.

The concentration of the solution is 15 mM, which anticipates "about 10 mM to about 500 mM" recited in instant claim 47. The acetonitrile solution is evaporated to dryness, and in this process the concentration of DOTMA would increase. In the evaporation process, the concentration would reasonable reach values above 15 mM, including values between about 25 mM to about 500 mM” (instant claim 48) and “about

100 mM to about 500 mM" (instant claim 49). Thus, the concentrations inherently present in the process of evaporating the 15 mM DOTMA/acetonitrile solution to dryness anticipate these ranges.

Although the 15 mM DOTMA/acetonitrile solution does not have a further amphiphile or a stabilizing agent, these are optional components in instant claim 47. Instant claims 54-60 merely further limit these optional components and do not positively require that these components be present. Therefore, claims 54-60 are included in this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-51, 53-67, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5834012 ('012). '012 discloses a lipid-complexed camptothecin preparation (see abstract). The lipid is preferably DOTAP (N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride; a cationic amphiphile), the same lipid disclosed in instant claim 53 (see col 3, lines 50-51; col 4, line 56; Examples). DOTAP complexes well with camptothecin (see col 13, lines 64-66). The concentration of drug and the concentration of lipid are result effective parameters to the efficacy of the drug and the drug/lipid complex ratio may be from 2:1 to 25:1 w/w (see Example 1). The preparation in solution would be transparent, isotropic, and substantially homogenous.

The limitation "non-vesicular preparation" in Applicant's claims, and how to compare this limitation to the prior art, requires interpretation. In one study of '012, the drug/lipid complex was prepared in a solution of 8:1 chloroform:methanol. In this preparation of '012, which does not contain water, there would reasonably be no liposomes present (i.e. a non-vesicular preparation). Claim 47 recites "in an aqueous phase". It is unclear if this is a required claim limitation (see ***Claim Rejections - 35 USC § 112, Second Paragraph*** above). For the purposes of comparing the claims to

the prior art, the Examiner interprets “in an aqueous phase” in instant claim 47 to be optional.

Further regarding comparing the limitation of “non-vesicular preparation” to the prior art, in another study of ‘012, the drug/lipid complex is in water and the drug/lipid complex preferably comprises liposomes (see Example III). However, even the aqueous preparation of '012, which comprises liposomes, reads on Applicant's “non-vesicular preparation" within the meaning of the instant specification. Page 17, lines 8-9 of the specification defines “non-vesicular cationic preparation” as “a composition comprising at least one cationic amphiphile in an aqueous environment.” The aqueous drug/lipid complex of ‘012 comprises at least one cationic amphiphile in an aqueous environment and is therefore a “non-vesicular preparation” within the meaning of the instant specification.

‘012 does not disclose the range “about 10 mM to about 600 mM” cationic amphiphile (DOTAP) in instant claim 47 nor the narrower ranges disclosed in instant claims 48-49.

It would have been obvious to one of ordinary skill in the art to find these concentration ranges, through routine experimentation, as the concentration of lipid is a result effective parameter to optimizing the efficacy of the camptothecin preparation. '012 provides sufficient guidance for finding this range as it discloses desirable lipid to camptothecin ratios of 2:1 to 25:1 w/w. “’[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)". MPEP § 2144.05.

Although the lipid/drug complex of '012 does not necessarily require a further amphiphile or a stabilizing agent, these are optional components in instant claim 47. Instant claims 54-60 merely further limit these optional components and do not positively require that these components be present. Therefore, claims 54-60 are included in this rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL DICKINSON whose telephone number is (571)270-3499. The examiner can normally be reached on Mon-Thurs 9:00am-6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Paul Dickinson
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